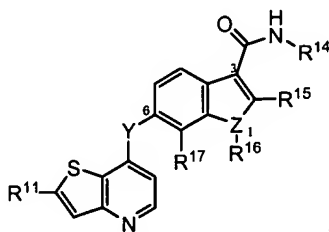


REMARKS

The present invention as defined by pending claims 52-103 is directed to N-substituted 3-carboxamido thienopyridine compounds of formula I:



wherein Y, Z, R¹¹, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are as described, or pharmaceutically acceptable salts or solvates thereof; pharmaceutical compositions containing these compounds; and methods of using these compounds and compositions in connection with vascular endothelial growth factor VEGF or FGF in proliferative disorders, kidney disease, angiogenesis, pancreatitis and blastocyte implantation.

Claims 52-103 are pending in this application. Claims 52, 72 and 76 are amended herein. Basis for these amendments is found throughout the specification and Examples as originally filed. No new matter has been added.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Office Action has rejected claims 80-101 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement as set forth on pages 2 and 3 of the Action. Applicant respectfully disagrees.

The present specification provides detailed procedures on how to make and use the claimed compounds of formula I, i.e., thienopyridine derivatives, pharmaceutical compositions and methods of using these compounds and compositions in connection with vascular endothelial growth factor VEGF or FGF in proliferative disorders, kidney disease, angiogenesis, pancreatitis and blastocyte implantation. Using these procedures as guidance, one of skill in the art (i.e., a trained scientist, usually with an advanced degree in chemistry or biology) would know how to make and use the claimed compounds and compositions in these methods. Applicant has provided 140 detailed working examples in the specification that describe the synthesis of the claimed compounds and compositions. The specification also provides detailed procedures and assays for testing the biological activities of these compounds and compositions.

Page 2 of the specification cites several references which were incorporated by reference into the specification, and copies of which were submitted with the parent application on Information Disclosure Statement Form 1449, dated November 18, 2003. These references and the four other art references Applicant submitted in the parent case, discuss the role of vascular endothelial growth factor VEGF or FGF in proliferative disorders, kidney disease, angiogenesis,

pancreatitis and blastocyte implantation. Thus, the specification provides an enabling disclosure of the claimed compounds, compositions and methods of their use.

Applicant respectfully requests reconsideration and removal of this rejection.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Office Action has rejected claims 80-101 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for reciting the terms “hyperproliferative disorder,” “kidney disease,” “prevention,” and “disease related to vasculogenesis or angiogenesis” since the specific disorders are allegedly not defined. Applicant respectfully disagrees.

“Hyperproliferative Disorder”

The specification provides detailed information regarding the term “hyperproliferative disorder,” and also provides examples of specific disorders associated therewith. Beginning on page 18, lines 1-18, the specifications recites:

“The terms “abnormal cell growth” and “hyperproliferative disorder” are used interchangeably in this application.

“Abnormal cell growth”, as used herein, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition), including the abnormal growth of normal cells and the growth of abnormal cells. This includes, but is not limited to, the abnormal growth of: (1) tumor cells (tumors), both benign and malignant, expressing an activated Ras oncogene; (2) tumor cells, both benign and malignant, in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs. Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis. “Abnormal cell growth” also refers to and includes the abnormal growth of cells, both benign and malignant, resulting from activity of the enzyme farnesyl protein transferase.”

Thus, the claims 80-101 are not indefinite because the term “hyperproliferative disorder” and the specific disorders associated therewith, are defined in the specification.

“Kidney Disease”

The specification provides detailed information regarding the term “kidney disease” and also provides examples of specific disorders associated therewith. Beginning on page 12, lines 8-9, the specification recites that kidney disease includes “proliferative glomerulonephritis and diabetes-induced renal disease.” Thus, claims 86 and 97 are not indefinite because the term “kidney disease” and the specific disorders that are associated therewith, are defined in the specification.

“Prevention”

The Office Action has rejected claims 87 and 98 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for reciting the term “prevention,” since the degree of prevention is allegedly not defined. Applicant respectfully disagrees.

Given their ordinary meaning, one of skill in the art would know that the term “prevention of blastocyte implantation” in claims 87 and 98 is not a matter of degree.

“Disease Related to Vasculogenesis or Angiogenesis”

The specification provides detailed information regarding the term “disease related to vasculogenesis or angiogenesis,” and also provides examples of specific disorders associated therewith. Beginning on page 2, lines 8-12, the specification recites:

“Agents, such as the compounds of the present invention, that are capable of binding to or modulating the KDR/FLK-1 receptor may be used to treat disorders related to vasculogenesis or angiogenesis such as diabetes, diabetic retinopathy, age related macular degeneration, hemangioma, glioma, melanoma, Kaposi’s sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.”

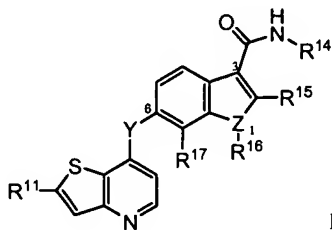
Thus, claims 88-90 and 99-101 are not indefinite because the term “vasculogenesis or angiogenesis” and the specific disorders that are associated therewith, are defined in the specification.

Applicant respectfully requests reconsideration and removal of these rejections.

Rejection of Claims Under 35 U.S.C. § 103(a) Over Munchhof et al. (WO 99/24440)

The Office Action has rejected claims 52-71 and 80-103 under 35 U.S.C. § 103(a) as allegedly being obvious over Munchhof et al. (WO 99/24440). Applicant respectfully disagrees.

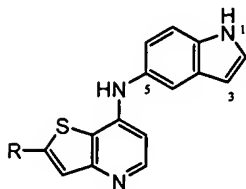
The instant claims distinguishes over Munchoff by claiming **N-substituted 3-carboxamido-6-indolyl thienopyridine** compounds of formula I:



wherein Z is N; and Y, R¹¹, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ are as described therein.

Munchoff does not disclose, teach or suggest any N-substituted 3-carboxamido-6-indolyl thienopyridine compounds. Instead, this reference teaches 5-indolyl thienopyridine compounds, wherein the indolyl ring is optionally substituted with 1 to 5 R⁵ substituents, wherein each R⁵ is independently selected from a group of over 30 different substituents.

Furthermore, Examples 48 to 60 of this reference are 5-indolyl thienopyridine compounds of formula:



wherein R is as described therein.

Munchoff does not teach or suggest modifying the 5-indolyl thienopyridine compounds taught therein to arrive at the instantly claimed class of N-substituted 3-carboxamido-6-indolyl thienopyridine compounds. Absent a teaching or suggestion in the prior art, one of skill in the art would not have been motivated to make the instantly claimed class of compounds. Thus, the differences between the teachings of this reference and the claimed class of compounds would not have been obvious to one of ordinary skill in the art at the time of invention.

Applicant respectfully requests reconsideration and removal of this rejection.

Rejection Of Claims Under 35 U.S.C. § 103(a) Over Marx et al. (WO 03/000194)

The Office Action has rejected claims 52-75 and 79-103 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Marx et al. (WO 03/000194). Applicant respectfully disagrees.

In order to be prior art under 35 U.S.C. § 103(a), the art being cited against the Applicants must have been published before the priority date of the Applicants' patent application. In the present case, Applicants' priority date is June 14, 2002, the date on which the provisional application USSN 60/389,110 was filed. The cited art WO 03/000194 has an international publication date of January 3, 2003. Therefore, the rejection under 35 U.S.C. § 103(a) does not apply to the claims of the present application and should be withdrawn.

Conclusion

Applicant respectfully requests reconsideration and withdrawal of the outstanding objections and rejections, in light of the foregoing remarks.

Respectfully submitted,

Date: November 5, 2004

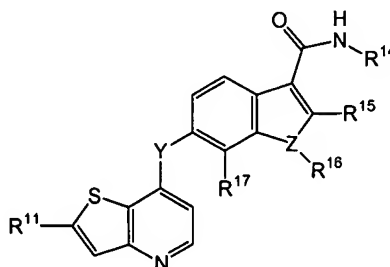
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Amendments to the Claims:

Please amend claims 52, 72 and 76 as follows (additions are in underline; deletions are in ~~strike through~~):

52. (Currently Amended) A compound represented by the formula I:



wherein:

Y is -NH-, -O-, -S-, or -CH₂-;

Z is -O- or -N-;

R¹⁴ is a C₁-C₆ alkyl, ~~amino~~ C₁-C₆ alkylamino, ~~hydroxy~~ C₁-C₆ alkylhydroxy, C₃-C₁₀ cycloalkyl, C₁-C₆ alkyl C₃-C₁₀ cycloalkyl or methylureido group;

R¹⁵ and R¹⁷ are independently H, halo, or a C₁-C₆ alkyl group unsubstituted or substituted by one or more R⁵ groups;

R¹⁶ is H or a C₁-C₆ alkyl group when Z is N, and R¹⁶ is absent when Z is -O-;

R¹¹ is H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -C(O)NR¹²R¹³, -C(O)(C₆-C₁₀ aryl), -(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_i(5 to 10 membered heterocyclic), -(CH₂)_iNR¹²R¹³, -SO₂NR¹²R¹³ or -CO₂R¹², wherein said C₁-C₆ alkyl, -C(O)(C₆-C₁₀ aryl), -(CH₂)_i(C₆-C₁₀ aryl), and -(CH₂)_i(5 to 10 membered heterocyclic) moieties of the said R¹¹ groups are unsubstituted or substituted by one or more R⁵ groups;

each R⁵ is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -C(O)R⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -NR⁶C(O)R⁷, -C(O)NR⁶R⁷, -NR⁶R⁷, -OR⁹, -SO₂NR⁶R⁷, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₁-C₆ alkylamino, -(CH₂)_jO(CH₂)_qNR⁶R⁷, -(CH₂)_iO(CH₂)_qOR⁹, -(CH₂)_iOR⁹, -S(O)_j(C₁-C₆ alkyl), -(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_i(5 to 10 membered heterocyclic), -C(O)(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_iO(CH₂)_j(C₆-C₁₀ aryl), -(CH₂)_iO(CH₂)_q(5 to 10 membered heterocyclic), -C(O)(CH₂)_i(5 to 10 membered heterocyclic), -(CH₂)_jNR⁷(CH₂)_qNR⁶R⁷, -(CH₂)_jNR⁷CH₂C(O)NR⁶R⁷, -(CH₂)_jNR⁷(CH₂)_qNR⁶C(O)R⁸, (CH₂)_jNR⁷(CH₂)_iO(CH₂)_qOR⁹, -(CH₂)_jNR⁷(CH₂)_qS(O)_j(C₁-C₆ alkyl), -(CH₂)_jNR⁷(CH₂)_iR⁶, -SO₂(CH₂)_i(C₆-C₁₀ aryl), and -SO₂(CH₂)_i(5 to 10 membered heterocyclic), the -(CH₂)_q- and -(CH₂)_i- moieties of the said R⁵ groups optionally include a carbon-carbon double or triple bond, and the alkyl, aryl and heterocyclic moieties of the said R⁵ groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R⁸, -C(O)OR⁸, -OC(O)R⁸,

-OC(O)OR⁸, -NR⁶C(O)R⁷, -C(O)NR⁶R⁷, -(CH₂)_tNR⁶R⁷, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_t(C₆-C₁₀ aryl), -(CH₂)_t(5 to 10 membered heterocyclic), -(CH₂)_tO(CH₂)_qOR⁹, and -(CH₂)_tOR⁹;

each R⁶ and R⁷ is independently selected from H, OH, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_t(C₆-C₁₀ aryl), -(CH₂)_t(5 to 10 membered heterocyclic), -(CH₂)_tO(CH₂)_qOR⁹, -(CH₂)_tCN(CH₂)_tOR⁹, -(CH₂)_tCN(CH₂)_tR⁹ and -(CH₂)_tOR⁹, and the alkyl, aryl and heterocyclic moieties of the said R⁶ and R⁷ groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, -C(O)R⁸, -C(O)OR⁸, -CO(O)R⁸, -OC(O)OR⁸, -NR⁹C(O)R¹⁰, -C(O)NR⁹R¹⁰, -NR⁹R¹⁰, C₁-C₆ alkyl, -(CH₂)_t(C₆-C₁₀ aryl), -(CH₂)_t(5 to 10 membered heterocyclic), -(CH₂)_tO(CH₂)_qOR⁹, and -(CH₂)_tOR⁹, where when R⁶ and R⁷ are both attached to the same nitrogen, then R⁶ and R⁷ are not both bonded to the nitrogen directly through an oxygen;

each R⁸ is independently selected from H, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_t(C₆-C₁₀ aryl), and -(CH₂)_t(5 to 10 membered heterocyclic);

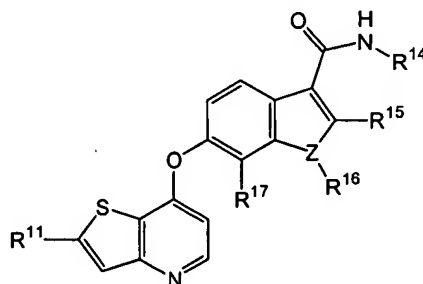
t is an integer from 0 to 6; j is an integer from 0 to 2; q is an integer from 2 to 6;

each R⁹ and R¹⁰ is independently selected from H, -OR⁶, C₁-C₆ alkyl, and C₃-C₁₀ cycloalkyl; and

each R¹² and R¹³ is independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_t(C₃-C₁₀ cycloalkyl), -(CH₂)_t(C₆-C₁₀ aryl), -(CH₂)_t(5 to 10 membered heterocyclic), -(CH₂)_tO(CH₂)_qOR⁹, and -(CH₂)_tOR⁹, and the alkyl, aryl and heterocyclic moieties of the said R¹² and R¹³ groups are unsubstituted or substituted with one or more substituents independently selected from R⁵, or R¹² and R¹³ are taken together with the nitrogen to which they are attached to form a C₅-C₉ azabicyclic, aziridinyl, azetidiny, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C₅-C₉ azabicyclic, aziridinyl, azetidiny, pyrrolidinyl, piperidiny, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl rings are unsubstituted or substituted with one or more R⁵ substituents, where R¹² and R¹³ are not both bonded to the nitrogen directly through an oxygen;

or pharmaceutically acceptable salts or solvates thereof.

72. (Currently Amended) A compound represented by the formula II:



II

wherein:

Z is -O- or -N-;

R¹⁴ is a C₁-C₆ alkyl, ~~amino~~ C₁-C₆ alkyl**amino**, ~~hydroxy~~ C₁-C₆ alkyl**hydroxy**, C₃-C₁₀ cycloalkyl, ~~C₁-C₆ alkyl~~ C₃-C₁₀ **cycloalkyl** or methylureido group;

R¹⁵ and R¹⁷ are independently H, halo, or a C₁-C₆ alkyl group;

R¹⁶ is H or a C₁-C₆ alkyl group when Z is -N- and R¹⁶ is absent when Z is -O-;

R¹¹ is a heteroaryl group unsubstituted or substituted by one or more halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -C(O)R⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -NR⁶C(O)R⁷, -C(O)NR⁶R⁷, -NR⁶R⁷, -OR⁹, -SO₂NR⁶R⁷, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_iO(CH₂)_qNR⁶R⁷, -(CH₂)_iO(CH₂)_qOR⁹, -(CH₂)_iOR⁹, -S(O)_j(C₁-C₆ alkyl), -(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_i(5 to 10 membered heterocyclic), -C(O)(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_iO(CH₂)_j(C₆-C₁₀ aryl), -(CH₂)_iO(CH₂)_q(5 to 10 membered heterocyclic), -C(O)(CH₂)_i(5 to 10 membered heterocyclic), -(CH₂)_jNR⁷(CH₂)_qNR⁶R⁷, -(CH₂)_jNR⁷CH₂C(O)NR⁶R⁷, -(CH₂)_jNR⁷(CH₂)_qNR⁹C(O)R⁸, -(CH₂)_jNR⁷(CH₂)_iO(CH₂)_qOR⁹, -(CH₂)_jNR⁷(CH₂)_qS(O)_j(C₁-C₆ alkyl), -(CH₂)_jNR⁷-(CH₂)_iR⁶, -SO₂(CH₂)_i(C₆-C₁₀ aryl), and -SO₂(CH₂)_i(5 to 10 membered heterocyclic), the -(CH₂)_q- and -(CH₂)_i- moieties of the said R⁵ groups optionally include a carbon-carbon double or triple bond, and the alkyl, aryl and heterocyclic moieties of the said R⁵ groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R⁸, -C(O)OR⁸, -OC(O)R⁸, -OC(O)OR⁸, -NR⁶C(O)R⁷, -C(O)NR⁶R⁷, -(CH₂)_iNR⁶R⁷, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_i(5 to 10 membered heterocyclic), -(CH₂)_iO(CH₂)_qOR⁹, and -(CH₂)_iOR⁹;

each R⁶ and R⁷ is independently selected from H, OH, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_i(5 to 10 membered heterocyclic), -(CH₂)_iO(CH₂)_qOR⁹, -(CH₂)_iCN(CH₂)_iOR⁹, -(CH₂)_iCN(CH₂)_iR⁹ and -(CH₂)_iOR⁹, and the alkyl, aryl and heterocyclic moieties of the said R⁶ and R⁷ groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, -C(O)R⁸, -C(O)OR⁸, -CO(O)R⁸, -OC(O)OR⁸, -NR⁹C(O)R¹⁰, -C(O)NR⁹R¹⁰, -NR⁹R¹⁰, C₁-C₆ alkyl, -(CH₂)_i(C₆-C₁₀ aryl), -(CH₂)_i(5 to 10 membered heterocyclic), -(CH₂)_iO(CH₂)_qOR⁹, and -(CH₂)_iOR⁹, where when R⁶ and R⁷ are both attached to the same nitrogen, then R⁶ and R⁷ are not both bonded to the nitrogen directly through an oxygen;

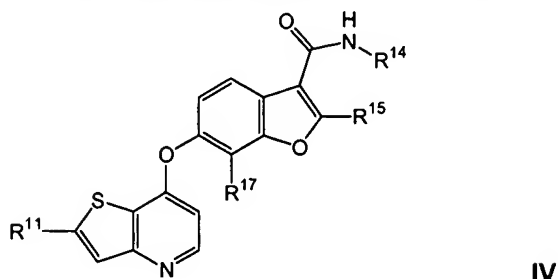
each R⁸ is independently selected from H, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_i(C₆-C₁₀ aryl), and -(CH₂)_i(5 to 10 membered heterocyclic);

each R⁹ and R¹⁰ is independently selected from H, C₁-C₆ alkyl, and C₃-C₁₀ cycloalkyl;

t is an integer from 0 to 6; j is an integer from 0 to 2; q is an integer from 2 to 6;

or pharmaceutically acceptable salts or solvates thereof.

76. (Currently Amended) A compound represented by the formula **IV**:



wherein:

R^{14} is a C_1 - C_6 alkyl, ~~amino~~ C_1 - C_6 alkylamino, ~~hydroxy~~ C_1 - C_6 alkylhydroxy, C_3 - C_{10} cycloalkyl, C_1 - C_6 alkyl C_3 - C_{10} cycloalkyl or methylureido group;

R^{15} and R^{17} are independently H, halo, or a C_1 - C_6 alkyl group;

R^{11} is a heterocyclic or a heteroaryl group unsubstituted or substituted by one or more groups selected from $-C(O)OR^8$, C_1 - C_6 alkyl, and $-(CH_2)_tOR^9$;

each R^8 is independently selected from H, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), and $-(CH_2)_t(5 \text{ to } 10 \text{ membered heterocyclic})$;

each R^9 is independently selected from H, C_1 - C_6 alkyl, and C_3 - C_{10} cycloalkyl; and

t is an integer from 0 to 6; j is an integer from 0 to 2; q is an integer from 2 to 6;

or pharmaceutically acceptable salts or solvates thereof.